BULLETIN
OF
THE JOHNS HOPKINS HOSPITAL

(THE PUBLICATION OF THE MEDICAL SCHOOL AND HOSPITAL)

(SUPPORTED BY THE DE LAMAR FUND OF THE JOHNS HOPKINS UNIVERSITY)

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THE JOHNS HOPKINS PRESS
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William Henry Howell

UNIV. OF MICH.

ADDRESS ON THE OCCASION OF THE PRESENTATION OF THE HOWELL PLAQUE TO THE JOHNS HOPKINS UNIVERSITY, JUNE 9, 1931

JOHN M. T. FINNEY

Mr. President, Ladies and Gentlemen:

In discharging the pleasant but difficult task of properly evaluating the many admirable qualities of him whom it is desired to honor, one is sorely tempted to cast aside proprieties, and run the risk of offending good taste by indulging in superlatives. But what else can one do when confronted by overwhelming evidence from all sources, that in the person of Dr. Howell we have to do with a man quite out of the ordinary. Colleagues at home and abroad, associates, students, friends, all unite in proclaiming him a man possessed of rare qualities, such as are seldom combined in a single individual. His winsome personality and charm of manner, his kindly consideration and unfailing courtesy, endear him to all alike, while his quiet dignity, his clearness of vision, lucidity of expression, preëminent sanity and uncompromising honesty, together with his complete mastery of his subject, make his scientific writings models of their kind, and his lecture hours seasons of intellectual pleasure and profit to his students. But notwithstanding the large measure of success that Dr. Howell has achieved as author and lecturer, it is perhaps as an investigator and contributor to scientific knowledge, as an inspiring teacher and trainer of men that he excels. It is given to but few to attain distinction in two branches of science. After having devoted his earlier years to physiology, in which he became universally recognized as a leading authority, Dr. Howell has in recent years devoted his attention largely to the study of hygiene and public health, a field in which he has achieved equally brilliant success.

Dr. Howell has been connected with this University since 1878. Entering as an undergraduate student at that time, he received the degree of Bachelor of Arts in 1881. He then joined that brilliant group of young men who surrounded Newell Martin in the Biological

Laboratory, and in 1884 was awarded his Doctorate in Philosophy. He immediately received an appointment as Associate in Biology, and later as Associate Professor.

Leaving the University in 1889, he went first to Michigan, then to Harvard, returning to Johns Hopkins in 1893 to become Professor of Physiology in the newly organized Medical School, where he continued his work until the organization of the School of Hygiene and Public Health in 1916. He then became Professor of Physiology and Assistant Director of that School, and had a large part in its organization and successful development. On the retirement of Dr. Welch in 1925, Dr. Howell succeeded him as Director.

Not the least of Dr. Howell's contributions to medicine were his influence and guidance in the development of the Johns Hopkins Medical School during the eleven years of his Deanship. The commanding position occupied by it today is due in no small measure to his wisdom and sound constructive judgment.

His scientific work, begun as an undergraduate student, has continued actively up to the present time. He has published more than fifty scientific papers; in the early years in Biology and Histology, and later in Physiology. His principal activity in research has been in the physiology of the circulation, and he has made important contributions to the knowledge of that subject, particularly in connection with the clotting of the blood. In the midst of an active life of research, teaching and administration, he has found time to prepare a textbook of Physiology, probably the best yet written, which has gone through eleven editions, and is now in use throughout the world. He has received honorary degrees from Michigan, Trinity, Washington University, Edinburgh and Yale. He is a member of the National Academy of Sciences and of the American Philosophical Society, and was President of the Thirteenth International Physiological Congress.

Mr. President, on behalf of the donors of this plaque, I now present it to the University. We believe that the distinguished sculptor, Dr. Maxwell Miller, has not only produced a work of real artistic merit, but has faithfully portrayed the features of our friend and teacher, whom it is a delight to honor.

In the entrance hall of the School of Hygiene and Public Health are two panels. One is already filled with a bronze relief of Dr. Welch.

It is the wish and hope of those presenting this plaque of Dr. Howell that it may occupy the other panel, as a companion piece to that of Dr. Welch, there to remain through the years to come, perpetual reminders to succeeding generations of students of the personalities and labors of these co-founders of the School of Hygiene.

METHODS AND MEDICINE[1]

WARFIELD T. LONGCOPE, M.D.

From the Medical Clinic, the School of Medicine, Johns Hopkins University and Hospital

One hears much discussion, nowadays, about science and the humanities, science and the practice of medicine, and science and the art of medicine; but it must occur to anyone who considers the matter, that misconceptions have arisen from placing these words in such sharp contrast. Their use in this particular manner does not imply, to most people, a close relationship of science, art and the humanities to medicine; but invites the assumption, if not the conclusion, that there are such fundamental differences in the intellectual processes concerned, that science, art and the humanities all form roads of approach which inevitably lead to divergent views of medicine in general. An effort has been made by many to refute the suggestion that science is in discord with the humanities and art, but the mere fact that such an attitude of mind exists, and needs refutation, is good reason for taking every opportunity to support those who, both by word and deed, have shown that science and art, the humanities and medicine, are in many aspects closely related in their development. It was Osler who said, "Twin berries on one stem, grievous damage has been done to both in regarding the Humanities and Science in any other light than complementary."

It has been stated, by some, that science is ruthless, cold and inhuman. Inasmuch as the aim of science is the search for truth, the prosecution of research cannot in its course pay much respect to conventionalities of thought or hold inviolate traditions of any kind. The results of scientific investigations may often oppose and offend current ideas and cherished opinions. Much the same can be said,

[1] Arranged from talks given before the Alpha Omega Alpha at the University of Rochester School for Medicine and Dentistry, May 22nd, 1931, and before the Harvard University Medical School, October 23rd, 1928. This latter address was published in *Human Biology*, December, 1929.

however, of new methods of expression by great artists. The music of Bach was almost incomprehensible to his generation, and certainly Wagner at first was not accepted with enthusiasm. The painting of Whistler and Manet offended the taste of their contemporaries, and Walt Whitman lived most of his life in obscurity. Everyone is familiar with the fact that the unexpected may remain unseen, and the strange and unusual, when forced upon our attention, may produce, at first, an unpleasant sensation. In this particular, then, there is little to choose between the two, for new knowledge arising from scientific investigation may disturb one's fixed ideas; while new methods of expression used in music, painting or poetry may offend one's aesthetic sense.

It has been repeatedly stated, and probably with considerable justification, that the application of knowledge derived through science is largely responsible for the "quantification, mechanization and standardization" which are said to characterize this country. It should be pointed out, however, that it is not the scientist, but the industrialist that is principally responsible for this turn of events, and if on the one hand there is evidence of the industrialization of science, there is, on the other, some effort in the direction of industrializing art.

Possibly if advances in science had remained simply as knowledge of natural phenomena, they would have been regarded in much the same light as the recent developments in astronomy and physical mathematics; extremely difficult for us to understand but partaking somewhat of the beauty and perfection of thought of a great poem. But not infrequently, this new knowledge, based upon pure experimental science, is unexpectedly found to be of economic value, and to the complete surprise, or even to the ignorance of the discoverer, the new knowledge, which originally may have been scarcely more than an abstraction, is used for some extremely practical purpose. It does not matter that the purpose is a worthy one, and rapidly results in increased comfort and material benefit to mankind; the fact remains that knowledge, gained through science, is, so to speak, industrialized, and thus becomes economically rather than intrinsically valuable.

Now it sometimes happens that the applications to which the fruits of science are put are mistaken for science itself. This is obviously a

misconception, for it is of little significance whether this knowledge, derived from science, is applied beneficently (for heat, light, etc.), or with evil intent (for wholesale destruction of life in war); science itself, which has a totally different goal, must be held innocent. Art stands to the crafts in somewhat this same relation. It is, therefore, justifiable for our purpose to consider science, divorced from utilitarian purposes, in a category with art and the humanities; and to place applied science in a second category which relates it more closely with the crafts.

Since medicine is one of the oldest sciences, it behooves us to consider what position it occupied in the greatest civilization of the ancient world. I need only remind you that Aesculapius was the son of Apollo to indicate that medicine and the sense of beauty were closely related in the Greek mind. Since science, medicine and philosophy and art all reached a height of perfection in Greece, never attained again until the Renaissance, and in some respects never eclipsed, one may assume that these culturistic studies developed and flourished in accord and harmony. The love of truth, accurate observation of natural phenomena, a sense of proportion and of beauty and the creative mind are all feebly descriptive of the age. Indeed they are not only descriptive of this age but of all ages in which medicine has thrived and grown. One of the greatest contributions of the Renaissance, it has always seemed to me, was the reintroduction of the experimental method, and the clear conception that experimentation could be employed in the study of natural phenomena. Before this time the quality of mind which empowers one to construct the well controlled experiment to test hypothesis, though not unknown, must certainly have been in abeyance. With the revival of Greek learning and the intense interest in natural phenomena and the physical world, there developed and grew this extraordinary mental quality which expanded descriptive science into experimental science, thus rendering it intellectually creative in somewhat the same sense that art is creative.

Leonardo da Vinci is one of the first and most brilliant examples in the Renaissance of the combination of artist, scientist, experimenter and, I should think, humanist. But there are many others who, during this period, when men became absorbedly and excitedly in-

terested in the world about them, investigated nature, experimented with natural phenomena, and attempted to express, by one means or another, the effect which the natural world produced upon them. This period of intellectual activity was no less important for science than for art, and culminated for medicine, according to Singer, in the experimental work of Harvey.

It is impossible, as Sarton has repeatedly said, to understand the present trend in the natural sciences unless one knows something of the past. This is especially true when one attempts to consider, even superficially, the relation of this field to human problems or to constructive intellectual processes. It seems clear, when regarded from this point of view, that during periods of naturalistic inquisitiveness, science and art have been so closely integrated in their growth that one scarcely ever thrives without the other; indeed one might almost say that one can scarcely survive without the other.[2]

An attempt must now be made to show how this preamble can be related to medicine in any of its practical aspects. To do this one must disregard the many economic questions which are of great importance in the practice of medicine. These form difficult obstacles for the physician as well as for the patient, and have attracted such widespread interest and sympathy that they have become not only the topic of many magazine articles but a subject for serious investigation and study by a national committee on the Cost of Medical Care. Nor can I pause to emphasize the need for expert craftsmanship in our own profession. Our enthusiasm for technical procedures, combined with a certain native facility, has led to the rapid development of elaborate and valuable mechanical methods which are practiced not infrequently with great dexterity and precision. If I may be pardoned for saying so, all these matters really represent the business and craftsmanship of our profession, and even though they are absolutely essential, they form only one part of clinical medicine in its broad and inclusive sense.

The phase of medicine, and of its practice, which I really want to

[2] Anyone interested in this subject should read the essay on "The Differences Between Art and Science in Their Relation to Nature" recently published in a book of essays by Dr. Alfred Cohn, entitled, "Medicine, Science and Art," University of Chicago Press, 1931.

emphasize is that which has to do with the intimate relation of the doctor to his patient, and how this is indissolubly connected with the investigation of disease itself. I cannot give you the fundamental principles upon which this is based in any better form than to quote a paragraph which many will recognize as coming from Osler:

> To wrestle from nature the secrets which have perplexed philosophers in all ages, to track to their sources the causes of disease, to correlate the vast stores of knowledge, that they may be quickly available for the prevention and cure of disease—these are our ambitions. To carefully observe the Phenomena of life in all its phases, normal and perverted, to make perfect the most difficult of all the arts, the art of observation, to call to aid the science of experimentation, to cultivate the reasoning faculty, so as to be able to know the true from the false—these are our methods. To prevent disease, to relieve suffering and to heal the sick—this is our work.

To observe the phenomena of life, to cultivate observation, to call to aid experimentation, to know the true from the false—these are surely the methods of science, and inasmuch as the doctor uses them, he employes science even in his daily routine work. When he adds to this a perfection in detail, a sense of proportion, and the ability to regard the problem as a whole, placing emphasis on those features that are of true importance, suppressing those matters that are secondary or that form but a background to the problem, he then becomes a true artist. It is not likely that he will become in either instance a creative scientist or a creative artist; for the creative imagination is rare indeed, but lacking this, he still works as a scientist with the sensitiveness of an artist.

In rare instances, however, the practicing physician becomes the creative scientist. His imagination conceives of an hypothesis, based on frequent, accurate, well controlled observation. This hypothesis is put repeatedly and rigidly to the test by carefully planned, albeit simple experiments on the human being. Many of the experiments of Harvey, the discovery of Jenner and the work of Laennec were of this type. But science, for most men, does not progress much beyond the descriptive method, and knowledge is sought and obtained by accurate observations of natural phenomena, recorded with meticulous care, collected, compared, controlled by further observations, subjected to critical analysis, and finally brought to a conclusion unin-

fluenced by desire or theory. This method results in what is commonly known as *experience*, a word interpreted in the Middle ages as signifying experiment, and used today by the French to describe experiment. But at times, in experience and during experiments, desire warps judgment, and the love of a theory leads to disaster.

The introduction to Arthus' book, "Anaphylaxie à l'Immunité," contains many good sayings, among which is the following: In comparing the theorist with the unbiased worker in science he says of the theorist:

> Blinded by his passion, that is to say by the immoderate love of his theory, he has recourse, in order to defend it, to all means, acceptable or not, for all means to him, have some good. He has ceased to be a man of science, he is a man of prejudice. Seek facts and coordinate them, you will be workers in science; devise or accept theories, you become politicians.

It is commonly said that through disease nature experiments constantly for us, but this can be scarcely accepted literally, for the kaleidoscopic picture that passes before us is not so much an experiment as a conflict of forces which for the observant physician results in an experience. An experiment must be conceived by the experimenter to answer a definite question, and so planned that ideally, except for the one variable, all other conditions remain unchanged. It is this matter of control that places all biological experimentation, and particularly experimentation in human disease, amongst the so-called inexact sciences. An experiment, therefore, depends more upon the thinking than the doing. It is only the lack of intellectual qualifications that prevents us from realizing that we perform an experiment every time we give a dose of castor oil. It is not the combination of circumstances, not the number of laboratories, not the amount of apparatus or the elaborateness of technique that is responsible for creative scientific investigation, for above and beyond all this it is the idea of the investigator that is of supreme necessity. Without creative ideas, all the accessories are useless.

We finally come to the second part of our thesis—the relation of the doctor to his patient as an artist and as a humanist. As doctors, our thoughts and energies are concentrated on the abnormalities of human beings. There is no separation of man from his disease or of disease

from man. The two are part and parcel of a single unit which needs some further definition for our purposes. What we recognize and classify as a disease picture is, in reality, the kaleidoscopic reactions of a man to some injury. This injury may take the form of invasion of the body by bacteria, the disturbance of the specific function of some organ (diabetes, Graves' disease), or a mechanical defect such as occurs in heart disease. In any event it is the patient, not the typhoid bacillus, that presents to us the disease called typhoid; it is the violently disturbed reaction of the patient to the abnormal action of the thyroid gland, not thyroxin, that gives us Graves' disease, and it is the more or less successful efforts of the patient to overcome a stricture of the mitral orifice, not the stenosis itself, that produces the picture called heart disease.

In the field of general medicine, in which we come more and more to think of morbid processes in terms of etiology, we have been prone to connect the morbid process with the parasite, the injury or the deformity rather than with the host. This is not surprising since our knowledge in this direction is constantly increasing; and since it is of prime importance that the antagonist should know, in the minutest particulars, the characteristics of his foe, any information gained in this direction is of inestimable value. As an outstanding and recent example of this progress, one need only recall the fine work of Avery and his associates on the pneumococcus, which has endowed this minute organism with such specific characteristics, such a complicated physiological existence, and such extraordinary powers of defence and of attack, that it now becomes evident that methods, hitherto unsuspected, must be devised to strip him of his armour, so that he may be helpless and made harmless to man.

But without the host there can be no disease. This image of disease as a reactive process is not by any means new. Indeed Stahl's whole conception of disease was that it represented a struggle between the animus and the noxious agent. The idea of disease, solely as a new physical state of being in a particular person, is still, nevertheless, incomplete, for one essential feature of this state is mental. The intellectual, the emotional, the spiritual qualities of the patient form an integral part of this disease state. When one speaks of the interaction between parasite and host, one must conceive of the host

as a living, thinking physical being controlled by appetites, hopes, fears, beliefs, and passions. As many modern philosophers and behaviorists insist, the body and mind are inseparable, although the idea of the body as one entity and the mind as another has existed for such ages, and is so deeply rooted that we have no word, as John Dewey says, to express this "wholeness of operation" or "unity in action." In an address sometime ago before the Academy of Medicine in New York, John Dewey said:

> There exists in present society, especially in industry, a large amount of activity that is almost exclusively mechanical; that is carried on with a minimum of thought and of accompanying emotion. There is a large amount of activity especially in "Intellectual" and "religious" groups in which the physical factor is at a minimum and what little there is is regretted as a deplorable necessity. But either sort of behavior in the degree of its one-sidedness marks a degradation, an acquired habit whose formation is due to undesirable conditions; each marks an approximation to the pathological, a departure from that wholeness which is health.

This quotation is quite as applicable to the physican as to the patient. The reaction of the body to disease is directed to the restoration or approximation of the wholeness of health, by destruction of the invading parasite, through satisfactory readjustment to a permanent injury or by temporary accommodation to a physiological disturbance. Each individual attacks his problem, both consciously and unconsciously, in a different manner; and though the common problems themselves are fairly limited in number and more or less familiar to us, each patient's method of attack or of resistance, which we call the disease picture, is marvelously and infinitely varied. This matter of attack or of resistance depends on a multitude of factors; race, inheritance, age, environment, experience, education all come into play; and as these factors work to differentiate one person from another, so they tend to individualize disease in each single patient. The intricate combinations, in any man, of anatomical, physiological, immunological and psychological attributes, so aptly termed by Draper the "panels of personality," together form the fertile, indifferent or resistant soil on which the noxious germ is sown or injury done. The disease picture, the pathological state, depends on the manner in which these forces overcome this noxious agent, resist it, or sink before the fatal injury.

To illustrate the point, we may consider two or three examples. The first should be an infection, and for simplicity's sake we will select that produced by *Bacillus typhosus*. The body of the young child is relatively resistant to this infection, and even though the germ gains entrance to the body, it may not find a soil favorable for growth. The less resistant may become infected, but the disease, as we say, is mild. The tissues overcome the germ, and neutralize its poison with comparatively little effort; the mind, less complicated in its mechanism than that of the adult, rests peacefully, and lets the tissues do their work successfully. In early adult life, and during pubescence, the body, for some reason, is more vulnerable, the reaction of the tissues more florid, and the psychic disturbances more violent; all of these transform the patient into a disease state that is called severe, dangerous, critical or hopeless. Finally, in old age, the body again becomes resistant, either from acquired immunity or from loss of favorable conditions for the growth of typhoid bacilli. The fire of youth has gone and if, by some peculiar chance, the body is invaded, the reaction of the tissues is sluggish and the temperature is low, but the mind, half clouded, wanders incessantly, subconsciously in delirium exposing the accumulation of years' experiences. In the three disease pictures, the morbid state would vary in the same person, if such a thing were possible, according to age, physical growth, experience and education.

As another example, one might select diabetes mellitus, primarily a disturbance in the function of a vital organ. Comparatively uncommon in the negro; said to be most common in the Jewish race; notoriously severe in children; strikingly mild in old age; influenced in many patients by their previous habits of eating, and the ease with which they put on weight; producing a craving for food that undermines the moral character; leading to neuritis in some older subjects; interfering with the natural growth and maturation of the youthful, the morbid state of diabetes mellitus assumes an individuality for each and every patient.

Just as no two human beings are precisely alike, not even twins from the same ovum, so two disease states can never be identical, even though they are produced by almost indistinguishable agents. Similarities do exist between disease states as well as between human

beings. This is most noticeable in twins, quite common in families, not rare in communities, unusual between nations and most divergent in different races. A single anatomical feature, too, a peculiar mode of thought, a simple physiological process or an isolated pathological lesion may seem to be exactly the same in two different individuals; but each complete personality, each state of disease, is unique.

When disease is regarded from this point of view, the slightest departure from the wholeness of health may produce a profound and lasting effect; for the significance of the injury may depend, not so much on its physical result, as on the interpretation that the patient gives it. A mild attack of vomiting may lead to years of misery, since the patient may regard it as an early sign of cancer; or a fleeting pain across the chest may breed the fear of heart disease which remains persistently for months. I once knew a woman who, when on her way home from Samoa, discovered a skin eruption on one hand. She was convinced that she had leprosy. When she arrived in this country the blemish had disappeared and its nature was never known. Though assured by her physicians that she was physically sound, she lived for years to all intents and purposes a leper.

One begins to understand, now, why a sense of proportion, why a knowledge of the wholeness of the patient plays an essential part in the doctor's attitude toward the patient; how without this sense of proportion, the true artistic sense, one gropes in the dark, sometimes inflicting wounds, and, in an effort to cure symptoms, leaves bruises worse than the malady itself. Indeed, most symptoms, as you know, are dependent solely on some interference or perversion of a physiological process; and though in many instances an anatomical lesion is responsible for the perversion of function, this is not always true. One person, for instance, vomits at a sickening sight as well as in cancer of the stomach. Tachycardia and palpitation are frequently referable to some psychic disturbance, while excitement and anger increase the blood pressure, and emotional conflicts cause a sense of great fatigue. Such abnormal sensations, in order to become symptoms, must first come into the field of consciousness; and consequently symptoms are in simple terms but part and parcel of the patient's cerebration. On the acuteness of this cerebration, furthermore, depend very largely the number and severity of the symptoms.

If the patient confined himself exclusively to accurate observation and precise description of his symptoms, our work would be much simplified; but for most patients this does not suffice. They forever seek an explanation for their sensations, and attribute their malaise or pains to indigestion, to some trouble with the heart, to cancer, or try at least to tag their symptoms with the familiar name of some disease. The one explanation that they shun most vigorously is the so-called nervous origin of their symptoms. They search invariably and continuously for a purely physical basis.

It is not my intension to discuss the purely emotional disturbances, the psychoneuroses; but I might refer to one example, which illustrates the fact that functional derangements of mind may masquerade as well defined diseases of somatic origin.

It is not uncommon to see, from time to time, a poor fellow relegated to chronic invalidism on account of symptoms, due entirely to the perverted function of some organ, and yet originating in emotional disturbance. When the symptoms are indicative of a serious disorder and are combined with signs suggestive of actual disease of the organ, the solution of the problem becomes doubly difficult. Under happy circumstances, however, the cure of such an illness may sometimes be accomplished in a single conversation. I recall very well seeing a young man, several years ago, who had been kept flat in bed for six months on account of symptoms simulating those of heart disease. He had had severe palpitation, tachycardia and fainting attacks; and his physicians, hearing a systolic murmur over the precordium, had told him that he had serious heart trouble, and a limited number of years to live. A careful examination did not convince me that he had any actual disease of the heart, and in conversation, the patient, who was an intelligent man, insisted that he knew his heart was sound. The story of the onset of his symptoms revealed their origin. He had just been elevated to an important position in a bank, when, one morning, he found that the accounts of one of his assistants, who was also a friend and who was absent that day, had been falsified, and that the assistant had absconded with a large sum of money. Greatly perturbed, he went out to lunch, and as he rose from the table to leave the restaurant he came face to face with a detective. Instantly, he had a violent attack of palpitation, and fainted outside the door of the

restaurant. During the ensuing investigation there were repetitions of these attacks, and, when his name was finally cleared and he was freed of all blame, he became so miserable that he sought medical advice with the result already told you. He had never before spoken of the incident in the restaurant or of his momentary terror. Fortunately, the solution of his problem was a simple one and unlike many others capable of solution by any practising physician. It required only an explanation of his misinterpretations and then reassurance. He threw away his digitalis, went to work, played golf and tennis and has been in excellent health ever since.

Often the busy doctor feels he has no time to spend long hours in conversation with a patient but occasionally such an interview might obviate much suffering, as well as many visits to the office or to the patient's home. Too often this form of approach is replaced by the deftness of craftsmanship, and the use of ingenious tools is substituted for a thoughtful consideration of the problem.

If such serious symptoms may arise solely from emotional disturbances, consider, for an instant, the deplorable plight of the poor fellow who has to wrestle, not only with an organic disease, but with his emotions as well. For, I suppose, it is fair to say that no patient suffering from an organic disease, unless his mind be clouded, is free from more or less emotional strain. Whether this depends on the readjustments made necessary by his actual state of illness, or whether it depends on a misinterpretation or improper estimate of symptoms, the emotional strain becomes an actual part of the disease, and has a definite bearing on its course.

There is one question that I rarely fail to ask a patient and that is "What do you think is the matter with you?" Occasionally the answer comes immediately "Is it anything like cancer, Doctor?" or "I thought I might have some trouble with my heart." More often the question is evaded, and a secret fear, of which the patient may actually be ashamed, is guarded more closely; yet with perseverance on may finally extract an embarrassed reply. Some of these fears and anxieties are well founded, others are preposterous and based on misinterpretations; but under any circumstances they must be taken seriously. When the doctor can truthfully dispel this fear, and it may require long and careful examinations and detailed explanations

to do so, he has rendered the patient a great service and perhaps even cured him of his symptoms.

In large part this emotional reaction is dependent on the nature of the patient. The introvert, or more especially the timid person, is prone to exaggerate each sensation and to give it undue importance; or to misinterpret the significance of symptoms and use them for some selfish purpose. The extroverts may have a nobler attitude. They disregard their symptoms, discountenance the importance of their illness, continue to perform their duties and interfere deplorably with the somatic efforts of adaptation to the injury. The course and picture of disease is thus affected and modified in a thousand different ways by the mental attitude of the patient. Our efforts to understand sickness and to relieve suffering must be directed to both mind and body and to the "wholeness" of the individual, where intellectual and emotional processes often need more attention than the physical.

Though each patient presents some such problem of either minor or major importance, the most serious situations arise, most naturally, in those afflicted with chronic disease. The impatience and irritation that any patient with heart disease may feel against a restraint, too rigidly enforced, often results in a physical agitation that may do more harm than intelligently graded exercises, with properly limited physical activity. This is especially true of the aged; and, when a cure is impossible, it is the duty of the physician to bring contentment, comfort or even happiness to his patients to lighten the burden of their affliction. But this does not mean necessarily that he should limit living to prolong life. As I grow older, I have less and less sympathy with the conscientious efforts merely to extend life in old age. The curtailment of activities, the tender nursing, the humane and assiduous attention of doctors are apt, too frequently, to carry the aged tottering by the danger point, and leave them helpless doddering wrecks of humanity. Having arrived at this stage, it seems beyond their power, or desire, to let go the one thing they possess, that shred of life that ties them uselessly to earth. The philosophy of Stevenson's "Aes Triplex" suits me better. He says, "We do not, properly speaking, love life but living." And again, "Does not life go down with better grace, foaming in full body over a precipice, than miserably straggling to an end in sandy deltas?" It is the duty of the doctor to

preserve, not only health and life, but joy of living; and if most of us had to make our choice we would take the latter. Why ward off death if in the attempt we kill living? But these, perhaps, are matters over which we have but slight control. The vigorously minded patient knows the hounds are in pursuit, and keeps up the chase in spite of our earnest protests and our pleadings to seek shelter.

It is not only in the chronic invalidism, and fatal diseases, that the patient needs more care than the disease needs treatment. The acutely ill also present similar problems for solution. Over and over again the convalescence from an acute illness is prolonged, or the health of the patient actually endangered through complications, because of his impatience to return to work. A single investigation soon shows that it is not the work he wants but money to pay his hospital expenses or the debts incurred by his family during his illness. Once these worries are relieved recovery promptly follows.

Indeed, the management of convalescence is worthy of a treatise in itself. As far as the friends, family and doctor are concerned, the illness has passed; the patient, though perhaps weak, is physically sound, and thus is heartily congratulated on his satisfactory and miraculous recovery and dismissed by all hands with rejoicing. The poor patient, on the other hand, now acutely aware of every disagreeable sensation, weary or exhausted in mind and body, unconsciously exaggerates these sensations, misinterprets his symptoms, undergoes agonies of fear lest he should not recover, or imagines he is left with some incurable result or that his illness is about to recur. Too tired to comprehend the logical reasoning of his friends and doctor, he drags on a miserable existence; until suddenly to his utter astonishment he does recover. It has often seemed to me that this period of profound unhappiness might be considerably shortened by proper reeducation of the mind as well as of the muscles of the body. In some conditions, there is a more subtle and profound disturbance of the mentality, that must be dealt with as an integral part of the disease, rather than as a natural quality of the patient. Aside from the actual psychoses, and the emotional disturbances attending almost any illness, one frequently observes slight alterations in personality, assuming so frequently the same form in each particular disease, that one comes to connect these mental aberrations with particular varie-

ties of illness. To illustrate, I may mention one or two examples: Any patient suffering from pernicious anemia may, during the exacerbation of his disease, become querulous, irritable and in general terms extremely disagreeable. He may actually have delusions of persecution. But as far as one can tell this is no fault of his, and he has no more control over his mental state than he has over his blood count. Nurses and doctors are sometimes prone to overlook this fact, and thus subject such patients to diciplinary measures that only make them worse. With recovery, however, many of these patients prove to be as sweet-tempered as you please, and then the nurse and doctor pride themselves on the excellent effect of their discipline. Another example is the peculiar delirium of typhoid.

Enough has been said to make clear that no study of disease, no therapeutic measure, can be undertaken without due regard to the personality of the patient. In almost every instance his mental makeup influences, in some way, the clinical course of the disease, while minute consideration of his character is often imperative if one wants to institute and carry forward successful therapeutic measures. On the other hand, one must recognize the fact that minor alterations in personality may be actually a symptom of the disease itself; and over these the poor sufferer has but slight control. One must regard them in the same light as edema of the feet in heart disease, or loss of weight in diabetes mellitus.

Perhaps you think, as students, that you have not time or opportunity to devote yourself to patients in this particular manner and with such elaboration of detail. The hours are short, the desire to become acquainted with a multitude of pathological lesions in the human subject is great, and the routine of the dispensary or ward affords few occasions for conversations with patients.

Not only in institutions, but in the office of the busy modern practitioner, or specialist, an efficient routine, too often, supplants or at least discourages the personal recognition that the patient needs and craves. The situation recalls a story, as I remember told by Kipling. A murderer, who got off with a life sentence, when asked what had impressed him most at the trial, replied that it was the frank boredom of all who took part in the trial. "You come to 'em," he said, "full of your affairs and then find it's only part of their daily work to

them." How frequently might patients think the same: One patient comes rushing impetuously to the office or hospital, bent on having the thing over with immediately, and ready, at any cost, to get at the bottom of his complaint; another, after days of indecision, finally screws up his courage to the point of entering timorously the doctor's office or the dispensary, terrified lest his worst fears be realized at this fateful visit. Under any circumstances, each patient considers his complaint as one of great peculiarity or perhaps obscurity, demanding prompt attention. When clerks and secretaries regard the situation as commonplace it is bad enough, but if the doctor, fagged perhaps by a hard day's work, does not show a spark of sympathy or understanding, the visit becomes a flat failure, and, for all the good most patients get, they might as well use a penny slot machine.

Most patients long for someone to whom they can confide their troubles. For this they look to the doctor, and it makes little difference whether he is clerk, interne or practitioner so long as he is the right sort. It may only be necessary for students to have recourse to a simple conversation; to show real interest in this man or that woman, as an individual, in order to let loose a flood of starling confidences. At other times the way is not so clear, suspicions and fears must be allayed before the friendly relations can be established. And then there comes, little by little, or sometimes in torrents, a more or less disjointed story, which, when pieced together, gives the record of a human life surprisingly valuable, at times, in disclosing an explanation for the actual physical ailment. You thus increase your knowledge of human nature, often learn a way to help the patient in his distress, and in addition gain a friend.

Pope has said that the "proper study of mankind is man," and even though the clinician has science, art and craftsmanship, unless he is intensely interested in human beings he is not likely to be a good doctor. At bottom, we all have many qualities in common, and these fundamental properties can be observed with somewhat less effort on our part in the clientele of a hospital, than in those members of society who are more deeply imbued with the "herd instinct," as Trotter calls it, or are protected by inherited conventionalities of thought and conduct. If we turn our attention, for an instant, from

the study of the abnormal organ or pathology, to the study of the morbid patient as a whole, the scope of clinical medicine widens, and takes on a character that differentiates it from all other arts and sciences.

The study of the patient must of necessity be prosecuted in a special manner. The relationship between doctor and patient partakes of a peculiar intimacy. It presupposes on the part of the physician not only knowledge of his fellow men but sympathy. He sits, not as a judge of morals and of conduct, but rather as an impersonal repository for confession. The patient, on his part, must feel the need of aid, and few patients come to doctors except with this incentive. This aspect of the practice of medicine has been designated as the art; yet I wonder whether it should not, most properly, be called the essence.

Each patient is a suffering, sensitive, thinking disease personality, not simply a sack of abnormal organs; each patient has his own peculiar problem to be solved. Undue concentration either on the physical defects, on the one hand, or on the emotional conflict, on the other, leads us inevitably to a degraded point of view. It is only when we understand the unity of patient and his illness that we can hope to cure successfully, relieve suffering or bring consolation to the sick.

PELLAGRA

Analysis of 102 Cases[1]

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From the Medical Service of the Baltimore City Hospitals

This analysis of our cases of pellagra was undertaken primarily because of the relative increase of the disease in recent years, and also to see if there were any foundation for the impression held by some that post-alcoholic pellagra is different from the type.

The fact that pellagra is constantly present among us is apt to escape attention, but those who see the material of a large public clinic drawn from the less favored elements of the population will be convinced that this disease still plays an appreciable part in the annual morbidity.

This is not the place nor the time to discuss the history of pellagra, although it is intensely interesting (1, 2). Suffice it to say that the condition has been recognized clinically for two hundred years, and that most of the ideas of its origin have centered about the diet. Our predecessors considered it as due to some bad or toxic element added to the food, Indian corn or spoiled Indian corn being the agents mostly held at fault. The infectious theory of its origin propounded by Sambon never gained any great headway, as it was so soon displaced by the brilliant demonstration of Goldberger (3) and his coworkers that pellagra was a deprivation disease, and due to insufficient vitamins of the B group in the diet.

This study is based upon all the cases of pellagra seen on the Medical Service of the Baltimore City Hospitals from January 1, 1911 to December 31, 1930, where, in 16,572 admissions of a general medical character, there were 102 cases of pellagra, a gross incidence of 0.68 per cent. Uniformity of diagnosis is assured by the fact that the senior author has been in attendance upon the Service throughout this period and has seen practically all of the cases.

[1] Read before the Medical and Chirurgical Faculty of the State of Maryland, April 29, 1931.

In reviewing the material, the following method of recording the data was employed:

Age.....Sex.....Race.....Occupation.....Social Status.....
Residence.....Date of Admission.....
Presenting Symptom.....Duration.....Month of onset...
History of previous attacks.....
Diet preceding onset.....
Use of alcohol?.....Spree preceding onset?.....
Other disease.....
Distribution of skin lesions.....
Stomatitis.....
Diarrhea.....
Evidence of spinal cord lesions.....
Psychosis.....
Blood picture.....
Gastric analysis.....
Treatment.....
Result.....
Period of Hospitalization.....

It was apparent at once that, from the standpoint of associated conditions, the disease, as we see it, may be classified rather clearly into three categories; the simple pellagras, the post-alcoholic variety, and pellagra arising as a complication of some other preceding disease.

By the simple type, we designate cases probably due solely to dietary deficiency, and conforming to the classical type of the disease. Of these we had 31.

The second group, of 40 cases, seems to us definitely based on alcoholism, in that the cases developed toward the end of a prolonged debauch, or, occasionally, in individuals accustomed to a heavy daily intake of distilled liquors. This type of the disease has recently been recognized by several authors (4, 5), and it is noteworthy that it has become more prominent in the years since the enactment of the prohibition law. From January 1, 1911 to December 31, 1919, in 6478 admissions there were 24 cases of pellagra, a gross incidence of 0.37 per cent. Five of these (0.08 per cent) were of the alcoholic variety. From January 1, 1920 to December 31, 1930, in 10,274 admissions, there were 78 cases of pellagra, an incidence of 0.75 per cent, with 35 (0.34 per cent) of the alcoholic type. So, while the

gross incidence of alcoholic pellagra has risen from 0.08 per cent in the former period to 0.34 per cent in the latter, the incidence of the other varieties has risen only from 0.29 per cent to 0.41 per cent.

The third type occurs in the course of some other disease of a chronic character, associated with general debility. In this group there were 31.

In figure 1, the incidence with regard to age and sex is set forth, and the chart requires little comment. Race seemed of no importance, the slightly smaller number of cases in the colored corresponding to the smaller number of admissions of the colored race to the service. It was noticeable, however, that the maximum incidence of the

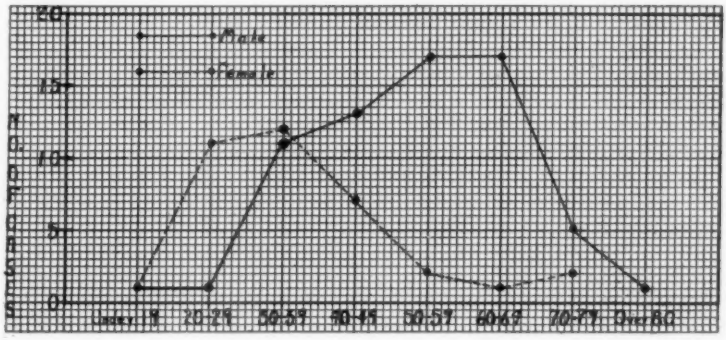

FIG. 1. INCIDENCE OF AGE AND SEX IN 102 CASES OF PELLAGRA

disease was at an earlier age in the colored than in the white. Age, sex and race reflected no differences between the alcoholic, the simple and the complicating types of the disease. Occupation, social status and residence revealed nothing. All of the patients had lived in Baltimore City.

The month of onset in figure 2 does not exhibit the striking autumnal recrudescence which is so much emphasized in the older writings. Again the three types of the disease fell exactly into line with each other, the alcoholic and complicating cases showing the same high incidence in the spring as the simple cases.

The complaint of the patient on admission was of skin lesions in

44 per cent (while actually present in 100 per cent), diarrhea in 16 per cent, sore mouth in 10 per cent, central nervous system changes in 8 per cent, while over 20 per cent were admitted with complaints which were not associated with the pellagrous lesions. No differentiation of a relationship between the presenting symptom and the etiological type of the disease was possible.

A history of previous attacks was obtained in only 14 cases, of which 6 were of the simple variety and 8 were alcoholic. Similarly, a definite history of a deficient dietary was obtained in only 9 cases, all of them

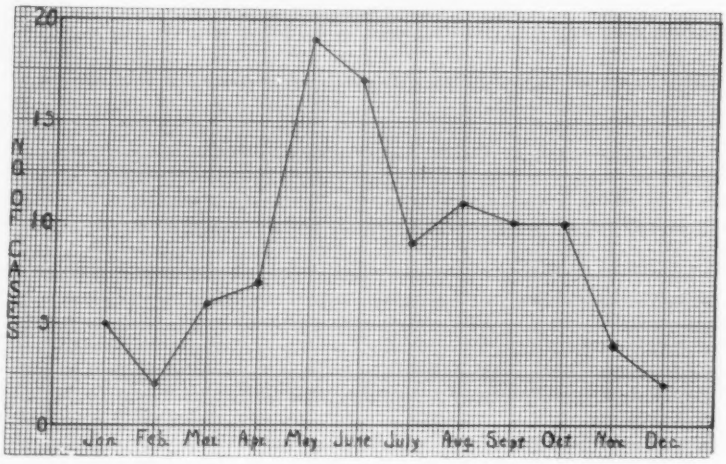

FIG. 2. MONTH OF ONSET IN 102 CASES OF PELLAGRA

of the simple variety. The small figures in both of these groups must be due, in part at least, to the low position of our patients in the social and intellectual scales, and to linguistic difficulties.

Of the 40 cases in which the history of alcohol was definite and clear cut, in 36 there was a story of a spree, which had lasted for some four to six weeks. Most of these patients were admitted either still intoxicated, or showing definite post-alcoholic manifestations. The remaining four had not been on a spree, but for long periods had been accustomed to a large daily intake of distilled liquors. (In

one case, upon reliable evidence, more than a quart of whiskey a day.)

The grave diseases in which pellagra was found as a co-existing or complicating malady are shown in table I. This type of the disease also has been recognized by others (6, 7) and must be, judging by our experience, much more common than is generally supposed.

The distribution of skin lesions was quite typical. In all cases the dorsum of the hands was involved. In 34 cases (33.3 per cent) there were perineal lesions, 23 in women and 11 in men, representing 67 per cent of the women, but only 17 per cent of the men. Similarly in 24 cases (23.5 per cent) there were typical lesions on the face and neck.

TABLE I

Diseases in which pellagra occurred as a complication (31 cases)

	NUMBER OF CASES
Pre-existing psychosis	11
Pre-existing diarrhea of unknown etiology preceding the skin lesions by more than 3 months	3
Hemiplegia with bulbar symptoms	3
Cachectic states:	
Carcinoma of gastro-intestinal tract	4
Diarrhea from disease of the rectum	4
Chronic nephritis	2
Pulmonary tuberculosis	2
Cirrhosis of the liver	1
Staphylococcus septicaemia	1

Thirteen patients (12.7 per cent) showed lesions about the elbows, and 9 (8.8 per cent) had changes over the feet.

Stomatitis of an appreciable degree was present in 76 cases (74.5 per cent) and in 12 cases (11.7 per cent) was complicated by the supervention of Vincent's Angina, which greatly increased the extent and severity of the buccal lesions, as well as the general severity of the disease. In the worst cases (usually in young negro women), the Vincent's lesion had invaded the rectum, vagina and perineal regions and were found even in the gastric and intestinal mucosa.

Diarrhea occurred in a severe form in 77 cases (76.6 per cent), and the combination of diarrhea and stomatitis was found 61 times or in 59.8 per cent of the total.

In none of these characteristic features was there detected any variation with reference to the type of the disease, the variability existing more with regard to the general severity of the malady.

The analysis showed 46 cases (45 per cent) with involvement of the spinal cord, which is in general like the subacute combined sclerosis of pernicious anaemia, though showing more tendency to implicate the posterior columns. The degree of involvement varied from diminution or loss of the knee-jerks, with subjective numbness and tingling, to severe combined sclerosis amounting to paraparesis or paraplegia with ataxia, paraesthesias and partial anaesthesia. Sphincter weakness or paralysis may occur in such cases. We had no instances of lower motor neurone lesions. There was little variation between the incidence for the three groups, it being 42.5 per cent for the alcoholic variety, 46.4 per cent for the simple type, and 45.1 per cent for pellagra arising as a complication. In all groups and equally true for each, the mortality rate was much higher for the cases manifesting cord changes than for those which did not.

The information concerning the psychoses is difficult to evaluate. Fifty-one patients, or 50 per cent, showed some type of psychosis, but, of these, only 26 (25.5 per cent) were thought to be pellagrous in their origin. Eleven of the remaining twenty-five had been under observation in the Psychopathic Hospital for periods varying from one, to five years, and had developed pellagra as a complication of the mental disease. The other 14 had typical alcoholic psychoses, such as delirium tremens, or Korsakow's syndrome. The psychosis of pellagra is of the acute hallucinatory type at the onset, and later tends to develop paranoid trends, with delusions supplanting the hallucinations. Its development is of grave prognostic significance.

The anaemia which was found in 81 cases (80.6 per cent) was of moderate degree and was secondary in type, with the haemoglobin about 75 per cent and the erythrocytes 3.5 to 4 millions. The leucocytes did not vary much from the normal except in the presence of intercurrent infections, and in only two cases was an eosinophilia noted. Here again differentiation of the influence of pellagra was made difficult on account of a multitude of extraneous influences, but it seemed that there was no essential difference in the blood pictures of the various types, except that the acute form of the alcoholic variety of the disease was a little less likely to show anaemia.

Some 90 per cent of the cases in which the gastric analysis is recorded showed an absence of free hydrochloric acid, and it was diminished in the remainder.

Caution should be used in making the diagnosis of pellagra without the typical manifestations, though the recognition of the disease presents little difficulty when, as is usually the case, characteristic lesions are present on the hands. This dermatitis on the hands is like a sunburn of severe type and involves the dorsum of the hand to the last interphalangeal joint and on the wrist is often continued around to the plantar surface like an encircling strap. It may be accompanied by vesicles or bullae, which are apt to become pustular, or the inflamed skin may dry and crack superficially with slightly bloody serous oozing. After healing, there is a corresponding area of pigmentation, which may persist for weeks or months. In the chronic cases, there is often a peculiar roughening of the knuckles suggesting sharkskin. Skin lesions of a character similar to that on the hands occur on nose, chin, malar eminences and forehead. Less frequently, the elbows, forearms, knees, shins and dorsum of the feet are involved in the dermatitis. Desquamation always follows the lesions.

Perineal and vulvar lesions occur for the most part only in the more severe cases and, as the location would indicate, are moist, macerated and associated with superficial or deep ulcers.

The tongue, buccal mucosa and pharynx may be deeply inflamed, exfoliated, or ulcerated, and extremely painful. This condition may render feeding so difficult as to contribute seriously to the gravity of the patient's illness.

When the acute phases of the lesions have disappeared, the diagnosis may often be determined by the persistent pigmentation, especially if accompanied by "sharkskin" on the knuckles. The demonstration of cord changes, slight or severe, the evidence of a residual glossitis, and the determination of achlorhydria are also of value as additional presumptive evidence in such cases.

Table II summarizes the incidence of the important clinical features of the disease.

Our experience with treatment may be considered typical. Prior to the definite association of a vitamin deficiency with the disease, the treatments employed were many and varied. Iron and arsenic were

the drugs most frequently employed, in the form of Blaud's pills, and Fowler's solution or sodium cacodylate. The diet, in our earlier cases, was given little attention.

In 1928, following the work of Goldberger (8) and of Minot and Murphy (9), a liver diet was first employed, and since that time has been used regularly. Table III shows the results in the uncomplicated

TABLE II

Incidence of principal clinical features in 102 cases of pellagra

	PER CENT
Complaint on admission:	
Dermatitis	44
Diarrhea	16
Stomatitis	10
C. N. S. changes	8
Other	2
Not related to pellagra	20
History of previous attacks	13.7
History of dietary deficiency	8.8
Distribution of skin lesions:	
Dorsum of hands	100
Perineum in men	17
Perineum in women	67
Face and neck	23.5
Elbows	17.7
Feet	8.8
Stomatitis	74.5
Diarrhea	76.6
Diarrhea and stomatitis	59.8
Spinal cord lesions	45
Psychosis	50
Psychosis referable to pellagra	25.5
Mild secondary anaemia	80.6
Gastric achlorhydria	90

cases in our series, and they speak for themselves, there having been no other change in the method of treatment. Not only has the percentage of recoveries been greatly increased, but the average stay in the hospital has been much reduced.

In the recent past, careful experimental work (10, 11, 12, 13) has shown a scientific basis for what, at the outset, was an empirical

method of treatment, and we now recognize that liver probably owes its potency to its high content of the Vitamin B complex.

We have used liver extract in only a few cases, but have found it fully as effective as liver itself. Dry brewers yeast is also a source of Vitamin B which has been used successfully elsewhere.

Many of the patients are so exhausted or lethargic, or have such pain in taking food, that the dietary treatment becomes a serious problem. It may be justifiable or even necessary to resort to tube-feeding with the addition of emulsified liver, or liver extract, in order to save life.

The dermatitis may be treated symptomatically, with caution to avoid oily or greasy applications because of their tendency to macerate the already inflamed skin. Dusting talcum or other soothing

TABLE III

Results of treatment in 71 uncomplicated cases

	WITHOUT LIVER DIET			WITH LIVER DIET		
	Number of cases	Per cent	Average hospital stay	Number of cases	Per cent	Average hospital stay
			days			*days*
Died	24	69	28	7	19.5	8
Recovered	9	26	56	25	69.5	32
C. N. S. residual	2	5	40	4	11.0	29
Total	35	100		36	100.0	

powder on the dry and cracked skin gives much relief. Sterile opening of the bullae will prevent pustulation and such cases do well when painted with a 5 per cent solution of gentian violet and left uncovered. The perineal lesions should be kept clean with douches of potassium permanganate or other non-irritating antiseptics, followed by dusting powder or gentian violet.

The stomatitis, especially when secondarily infected with Vincent's spirillum, demands careful treatment. Sodium perborate as a paste, or stronger solutions of potassium permanganate, if the former be too irritating, will usually control the situation. We feel local applications of neoarsphenamine to be unsafe, and in general care should be taken not to treat the lesions too vigorously.

Diarrhea often requires active measures. The usual agents (bismuth, opium, etc.) may be necessary in large amounts, but we have found that most of the cases, even when the diarrhea is severe, will respond almost specifically to liberal dosage with hydrochloric acid. This was true even in one case in which there was no gastric achlorhydria. In extreme cases, one gram of calcium chloride intravenously has been necessary as a last resort. As yet this has not failed to prove effective.

The cord changes are most obstinate, and no satisfactory treatment for them has been found. They do seem to respond to some extent to the long continued use of hydrochloric acid, and this drug is certainly to be recommended. In the light of the experience with the subacute combined sclerosis of pernicious anaemia, we are now trying massive doses of raw liver, but so far without apparent benefit.

The psychoses we have found entirely hopeless. Occasionally, improvement will take place as the other signs of the disease clear up, but failing this, nothing further is to be expected.

The anaemia will disappear on the liver diet, especially with the addition of iron. We recommend either Blaud's pills (90 to 120 grains per day) or iron ammonium citrate.

DISCUSSION

An important question arises from the striking association between severe alcoholism and pellagra. This post-alcoholic variety of the disease has been previously recognized and there has been much speculation concerning the relationship.

Three theories suggest themselves, but so far no experimental work has been adduced to prove or disprove any of them.

First, that the pellagrous manifestations are a result of deleterious elements (possibly some of the higher alcohols) present in the sophisticated beverages to which the victims are accustomed. This is in line with the suggestions of an alcoholic pseudopellagra (14), but is not substantiated by our experience. We feel that we have established the absolute identity of post-alcoholic pellagra and the simple form of the disease. For the dipsomaniac on a spree, the sources and types of his beverages are too varied to allow the postulate of a constant poisoning by a single foreign substance.

Second, that simple withdrawal of food, so common in alcoholics on a spree, is the etiological factor. This at first seems plausible, but does not serve to explain the group of cases seen in individuals who never go on a spree, but are accustomed to a large daily intake of alcoholic beverages.

The third theory, which to us seems more plausible, is that either alcohol itself destroys the pellagra-preventing factor in the gastro-intestinal tract, or that the gastro-intestinal tract is so altered by the large amount of alcohol that it is incapable of assimilating the pellagra-preventing factor.

This theory, too, is in line with the observation of the condition in association with debilitating diseases known to produce a disturbance of metabolism. In some of these, of course, the largest factor is inability or unwillingness to take food, but there remains a relatively large group in which the food intake is quite adequate, but in which pellagra will develop obviously because of inability to assimilate food. There is now under observation on our wards a patient with an inoperable carcinoma of the stomach who has developed pellagra while taking a liver diet, which had been given to keep control of his anaemia!

In conclusion, we should like to emphasize the occurrence of pellagra as a complication to cachectic states because, although it has been previously noted, it is unquestionably more common than is usually recognized.

SUMMARY

1. An analysis of 102 cases of pellagra is presented.

2. Thirty-one of the cases were of the simple variety; 40 were post-alcoholic, and in 31 cases the disease arose as a complication of some other malady.

3. The alcoholic variety of pellagra has become more than four times as common since the enactment of Prohibition.

4. The clinical features of the disease are pointed out, the diagnosis is discussed, and the observation is made that there exists no difference between the three types.

5. Treatment is considered, with particular emphasis on the value of the liver diet, the dry treatment of the skin lesions, and the not too vigorous treatment of the stomatitis.

6. Various theories as to the etiological relationship between alcohol and pellagra are considered.

7. The common occurrence of pellagra as a complication of debilitating disease is noted.

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HYPOPHYSECTOMY IN THE MONKEY (MACACUS RHESUS)

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At the request of Dr. Carl G. Hartman, of the Carnegie Institute of Embryology, we attempted the complete aseptic removal of the hypophysis in the monkey (Macacus Rhesus). This is rendered difficult by the position and configuration of the sella turcica, and by the overlying dura mater. This membrane spreads over the hypophysis completely, except for an aperture about 1 to 2 mm. in diameter through which the infundibulum passes. Beneath this roof of dura mater the hypophysis lies rather loosely attached in the rounded pocket of the sella. The usual operative procedure of pinching the stalk and lifting or curetting the gland out of the sella is impossible in the monkey without exerting very forceful retraction on the brain, with resultant trauma, and without enlarging the existing aperture in the dura, which is likely to cause hemorrhage. To avoid these undesirable consequences we attempted to aspirate the hypophysis by placing the tip of a suitably curved glass tube (pl. 1, fig. 4) in the existing opening in the dura. At first we tried the method on dead monkeys and found that the force exerted by a water suction pump attached to the hydrant was sufficient to remove the gland completely. We then applied this method to living monkeys about one year old and found it to be equally efficient. A description of the operative technic follows:

A monkey, weighing approximately 1700 gm., is given an ether anesthetic after a preliminary hypodermic of morphine (gr. $\frac{1}{8}$). The head is shaved and the field of operation is prepared with an acetone alcohol solution of mercurochrome. A slightly curved incision (pl. 1, fig. 1) is made about 1 cm. from the midline. The fascia covering the temporal muscle is incised about 3 mm. from its line of origin. A portion of the temporal muscle is divided and separated from the underlying bone with a periosteal elevator, and a defect measuring about 2 cm.

by 2.5 cm. is made in the bone. A flap of dura is incised and reflected anteriorly. Bleeding from the meningeal artery and from small venous communications between the dura and the cortex is controlled by crushing these vessels with a Halsted clamp. The exposed cortex (pl. 1, fig. 2) is covered with cotton moistened with warm normal salt solution, and the temporal lobe is gently retracted. There is a surprisingly large amount of cerebrospinal fluid in the brain of a one-year-old monkey, and as this is gradually pressed out and removed, one is able to compress and retract the temporal lobe so as to expose the crescentic edge of dura marking the lateral border of the sella (pl. 1, fig. 3). The third nerve is identified, and the carotid artery can be easily seen. To facilitate this exposure the head is rotated so that the hemisphere tends to fall away from the base of the cranial chamber.

The tip of a suitably curved glass tube connected with a water suction pump is placed in the small opening in the dura overlying the hypophysis. This aperture cannot be seen, but it is easily detected by passing the tip of the aspirating tube anterior to the third nerve and posterior to the carotid artery (pl. 1, fig. 5), and then rotating it about 90°. When this position is reached, suction is applied by placing one's finger over the opening in the side of the glass tube. Turning of the tube from side to side is not necessary, as suction alone brings out the loosely attached hypophysis. In nearly all cases the operator can see the hypophysis as it is drawn through the narrow portion of the glass tube, but it is wise to maintain suction for a minute or two after one thinks the sella is empty. The anterior and posterior lobes usually come out separately, the latter in one piece, the former in fragments. The glass bulb interposed between the aspirating tube and the water suction pump acts as a trap in which to catch the specimen. It is quite possible to empty the sella thoroughly without producing the slightest bleeding.

As soon as the operator thinks that all of the gland has been removed the tube is withdrawn and the wound filled with warm normal salt solution. The dural flap is spread over the cortex, but not sutured. The temporal fascia is reapproximated with interrupted sutures of fine silk, and the skin closed with inverted subcuticular sutures of fine silk. No dressing is placed over the incision.

This operative procedure has been attempted 25 times and success-

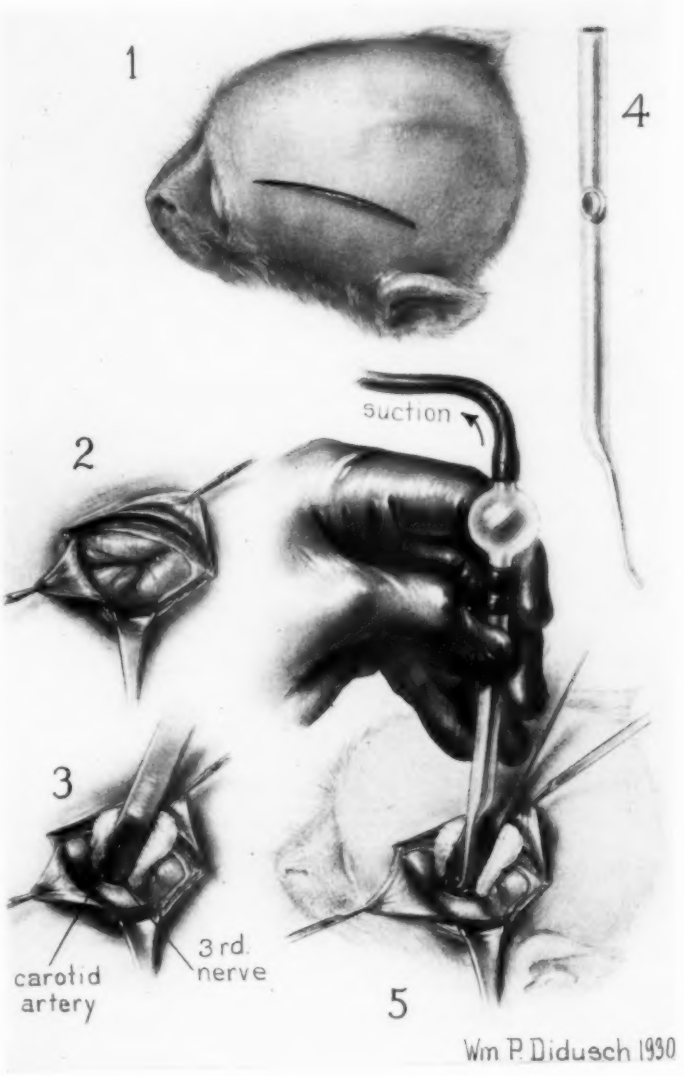
fully accomplished in all but six cases. One of the deaths was due to the anesthetic; the second was due to injury of the brain stem because the operator awkwardly passed the glass tube over the edge of the tentorium; and in the third instance an adult monkey died probably from hemorrhage around the base.[1] All of the wounds have healed *per primam*. In the first two cases the third nerve was severed in order to obtain better exposure, but it was soon learned that this is unnecessary. In each case the tissue removed has been studied histologically. The sections have shown that the posterior lobe generally comes out intact, whereas the anterior lobe comes out in fragments. This fact speaks strongly for the advantage of removal by suction rather than by the use of instruments. In one of the monkeys which died the region of the sella and overlying brain has been decalcified and serial sections have been prepared. Dr. F. C. Lee has examined these and reports that no remnants of the hypophysis, including the infundibulum, can be seen. In 6 of the 25 operations the animals used were adults. Their brains were much firmer and less compressible than those of the younger monkeys. The time required for the complete operation has varied from 30 to 65 minutes. A most interesting observation has been the speedy recovery that all of the young monkeys have shown. Within three hours after the operation they climbed about the cage and took food and fluids.

We have found that the utmost care must be exercised in giving the anesthetic. After the induction the ropes holding the monkey to the table are loosened and every effort is made to assure unrestricted respiratory excursion.

I wish to thank Mr. Michael Ullrich for the careful anesthetics he has given and Mr. T. C. von Storch for his suggestions and assistance.

[1] Three monkeys, all operated upon at the same time, died on the third day of meningitis.

PLATE 1


1
4
suction
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3
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FOETAL BLOOD STUDIES

III. The Chemical Nature of Asphyxia Neonatorum and Its Bearing on Certain Practical Problems

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There is considerable evidence that the onset of respiration at birth is conditioned by chemical, rather than by physical factors. Thus, the early theory of Preyer (1), which attributed this phenomenon to reflex stimulation of the respiratory center by the trauma of labor is hardly in keeping with clinical experience, since rough palpation, attempts at version and the application of forceps fail to initiate breathing as long as the foetus is *in utero* with the placental circulation intact. The view that skin irritation as the result of exposure to air and change of temperature causes the infant to breathe was refuted by Ahlfeld (2), who delivered several women in warm saline baths and found that respiration began as usual. It would seem, moreover, that if the first breath were due solely to reflex action, as these physical theories would postulate, the onset of respiration should occur simultaneously with delivery, instead of being delayed thirty seconds or more as it frequently is. Since theories based on physical stimulation, therefore, fail to furnish a rational explanation of the onset of respiration, attention in recent years has centered on biochemical interpretations of this phenomenon,—a trend which would seem only logical in view of the known chemical factors which influence respiration in the adult.

While the chemical control of respiration in extra-uterine life, however, is substantiated by an accumulation of exact, quantitative data, the mechanism by which this function is established at birth has received little direct study. The various chemical theories which have been advanced to account for the phenomenon have not been based on well attested facts of foetal physiology, but have been chiefly inferential in character. For instance, the view that the onset of

breathing is due to an increased carbon dioxide tension in the blood of the infant (3), although quite plausible, has not been supplemented by studies of the actual tension of this gas in foetal blood; similarly, the explanation of intra-uterine apnea on the basis of a low carbon dioxide tension is without factual substantiation.

Our knowledge concerning the chemical nature of asphyxia neonatorum is likewise meagre. In discussing this condition in 1925, Yandell Henderson (4), noted that "asphyxia is usually thought of as a condition of oxygen deficiency and excess of carbon dioxide. This," he continues, "is a misconception; asphyxia, usually, as in the typical condition of carbon monoxide poisoning, involves both low oxygen and low carbon dioxide content in the blood and tissues." More recently (5), he adds that "in the asphyxiated child, although there may be more carbon dioxide than normally, the center is so depressed that this stimulus is insufficient to excite natural breathing." These views are founded not only upon an extensive experience in the general physiology of respiration but also upon careful studies of asphyxia in carbon monoxide poisoning; as far as we have been able to determine, however, they are not supported by blood chemical data upon asphyxiated infants. In a quite recent paper, Coryllos (6) has advanced the view that asphyxiated babies present a real alkalosis to which the respiratory center responds by apnea, but has adduced no direct evidence that such an alkalosis does exist. The only direct studies on the blood of asphyxiated infants which have come to our attention are those of Kane and Kreiselman (7). These authors, after making the clinical observation that inhalation of oxygen is quite as efficacious as that of carbon dioxide in resuscitating asphyxiated babies, carried out studies in which it was shown that the carbon dioxide content of the blood of the new-born is consistently high and that the amount of this gas increases with the degree of asphyxia. They concluded, therefore, that the use of carbon dioxide as a resuscitating agent is contraindicated. In their brief preliminary report, Kane and Kreiselman chose to discuss only the carbon dioxide content of the blood at birth without mention of gas tensions, and they thus convey the impression that the blood carbon dioxide content itself influences respiration. It will be recalled, of course, that it is rather the carbon dioxide tension, or the actual amount of free carbonic acid in the blood, which is believed to be active in this connection.

It has seemed to us that the whole problem of the onset of respiration at birth, including asphyxia neonatorum, might be placed on a more satisfactory foundation if there were available quantatitive data on those constituents of foetal blood which may be concerned in the process. To this end, studies on the oxygen relationships (8) and on the lactic acid content (9) of umbilical cord blood under various conditions have already been published. The present paper reports a study of the carbon dioxide content, the carbon dioxide tension and the hydrogen-ion concentration of foetal blood in normal and in asphyxiated babies.

METHODS

Blood samples were obtained by venepuncture from the umbilical cord vessels and the maternal arm vein, the specimens being collected under oil in accordance with a technique which we have described elsewhere (8). But whereas one can readily secure from 10 to 20 cc. of blood from the umbilical vein by this procedure, it is difficult to obtain more than 5 cc. from the umbilical arteries; frequently, the amount available in these vessels is less than 3 cc. For this reason it has been necessary to omit pH determinations on umbilical artery blood in a considerable number of the cases in this series.

The pH of the serum was measured electrometrically with a Michaelis U electrode and on a Leeds and Northrup potentiometer; in a few of the more recent determinations a McClendon electrode was employed. Duplicate determinations were made on each sample with a precision of 0.01 pH.

The total carbon dioxide content of the whole blood (free plus combined carbon dioxide) was determined by the method of Van Slyke and Neill (10) in a calibrated, constant volume Van Slyke pipette. The oxygen analyses were also carried out by the Van Slyke and Neill method.

The carbon dioxide tension, or the partial gas pressure of the uncombined carbonic acid of the whole blood, was calculated from the pH and the total carbon dioxide content by the following formula (11):

$$CO_2 \text{ tension} = \frac{14.04\ CO_2}{\text{Antilog } (pH - 6.1)} \text{ mm. of mercury}$$

The lactic acid determinations were carried out by the method of Friedemann and Kendall (12).

THE CARBON DIOXIDE RELATIONSHIPS OF UMBILICAL CORD BLOOD IN NORMAL INFANTS AT BIRTH

It may be seen from table I that the carbon dioxide relationships of foetal blood differ consistently from those of maternal blood in

TABLE I

Showing the carbon dioxide relationships of foetal and maternal bloods under normal conditions

The majority of these patients were multiparae who had rapid, spontaneous deliveries without anaesthesia and whose babies cried vigorously shortly after birth. The specimens in Case 1 were obtained at Caesarean section just before the child was removed and may be taken as representing the carbon dioxide relationships of umbilical blood as they exist *in utero*; the operation was performed under infiltration anaesthesia.

CASE NUMBER	MATERNAL VEIN				UMBILICAL VEIN				UMBILICAL ARTERY			
	pH	CO_2 content	CO_2 tension	O_2 content	pH	CO_2 content	CO_2 tension	O_2 content	pH	CO_2 content	CO_2 tension	O_2 content
1	7.42	46.5	31.2	10.8	7.38	48.4	35.7	13.3	7.35	56.2	44.3	6.3
2	7.44	44.8	28.7	10.5	7.40	45.1	31.7	11.2		50.7		5.5
3	7.36	43.1	33.2		7.35	46.0	36.2	7.9	7.31	49.9	43.0	3.6
4	7.45	42.5	26.6	11.0	7.41	46.2	31.8			51.1		
5	7.38	40.3	29.8		7.38	47.7	36.0	8.7		52.5		2.7
6	7.40	42.5	29.8	13.3	7.36	41.8	32.0	12.1	7.34	46.9	37.8	6.0
7	7.33	44.6	37.0	9.1	7.27	47.4	44.8					
8	7.35	42.4	33.4		7.35	44.9	35.5					
Average...	7.39	43.3	31.2		7.36	48.4	36.1					

The figures for oxygen and carbon dioxide content are expressed as volumes per cent and those for carbon dioxide tension in mm. of mercury.

three respects. In the first place, the carbon dioxide content of the umbilical cord blood is higher than that of maternal blood; secondly, the pH is very slightly more acid; and thirdly, as a result of these two factors, the carbon dioxide tension of the foetal blood, particularly that of the umbilical artery blood, is definitely above that of the maternal blood. We shall presently desire to discuss these findings from the viewpoint of gaseous interchange in the placenta and it may be objected that in so doing our comparisons are based not on the maternal blood of the intervillous spaces but on blood from the ma-

ternal arm vein, and that conclusions derived from the study of the latter blood are not necessarily applicable to the blood in the intervillous spaces. Although this criticism is in general a valid one, in the specific instance under discussion we have taken, as representative of conditions in the mother, blood which is venous in character, whereas, to the best of our knowledge, the blood in the intervillous spaces is a mixture of arterial and venous bloods. Accordingly, had we been able to analyze the blood of the intervillous spaces, instead of that of the arm vein, we should presumably have found it more arterial in character, with consequently a lower carbon dioxide content, a higher pH and a lower carbon dioxide tension,—findings which would make the differences just described still more marked.

While the carbon dioxide tension of the umbilical vein blood is not markedly higher than that found in the blood of the maternal vein, the tension of this gas in the umbilical artery blood, that is, in the blood returning from the foetus, is decidedly more elevated. In fact, our studies on the latter blood make it possible to establish definite diffusion gradients in respect to carbon dioxide between the foetus and the mother. Thus, in Case I, shown in table I, the carbon dioxide tension of the umbilical artery blood was 44.3 mm. of mercury in contrast to a maternal carbon dioxide tension of 31.2 mm., a diffusion gradient from foetus to mother of 1.4:1; similarly, in Case No. 3, the gradient is 1.3:1 and in Case No. 6, 1.3:1. As shown in an earlier paper, the diffusion gradient between mother and foetus in respect to oxygen is much higher, being approximately 2:1. Since, however, the diffusion constant for carbon dioxide across a wet membrane is much greater than that of oxygen (13), the gradient of 1.3:1, which we have reported, seems ample to carry out the passage of carbonic acid from foetus to mother.

Our figures do not permit precise conclusions as to the carbon dioxide tension of the mixed blood which supplies the brain of the foetus, but Huggett (14), in studies on the goat, has shown that in the foetus of that animal the carbon dioxide tension of the carotid blood is approximately the mean of that of the two umbilical bloods. If the same holds true for the human, we may estimate the carbon dioxide tension of the blood supplying the foetal brain in the latter species as of the magnitude of 38 to 40 mm. of mercury. In any event, it

seems apparent from our results—and it is this we desire to emphasize—that the carbon dioxide tension of the mixed foetal blood, even under normal conditions, is definitely higher than that found in the venous blood of the mother.

THE OXYGEN AND CARBON DIOXIDE RELATIONSHIPS OF UMBILICAL CORD BLOOD IN ASPHYXIA NEONATORUM

The study of asphyxia neonatorum from a blood chemical viewpoint is complicated by the fact that most asphyxiated babies have been delivered by operative means with their mothers under varying de-

TABLE II

Showing the oxygen and carbon dioxide relationships of foetal blood in four normal infants who were delivered by forceps with the mothers under gas-oxygen-ether anaesthesia

All of these babies were crying vigorously within a minute after delivery.

CASE NUMBER	MATERNAL VEIN				UMBILICAL VEIN				UMBILICAL ARTERY			
	pH	CO_2 content	CO_2 tension	O_2 content	pH	CO_2 content	CO_2 tension	O_2 content	pH	CO_2 content	CO_2 tension	O_2 content
1	7.22	36.1	38.4	8.7	7.20	40.2	44.8	5.3	7.16	44.3	54.1	0.8
2	7.18	34.3	39.8	9.9	7.15	39.3	49.3	8.4	7.14	45.2	58.2	2.6
3					7.23	43.7	45.4	10.0				
4					7.22	37.1	39.4	5.5				
Average					7.20	40.1	44.8	7.3				

The figures for oxygen and carbon dioxide content are expressed as volumes per cent and those for carbon dioxide tension in mm. of mercury.

grees of anaesthesia. In order to evaluate chemical changes in the blood of these infants, therefore, it becomes necessary to establish those alterations which may be expected to result from the anaesthesia alone. To this end we have studied the carbon dioxide, as well as the oxygen relationships, of umbilical cord blood in a small series of normal, non-asphyxiated babies who were delivered by operative means from anaesthetized mothers. The general effect of anaesthesia on the foetus will be discussed in some detail in a following paper and it suffices here to point out that the foetus shows definite changes in the acid-base equilibrium of its blood as the result of maternal anaesthesia, and that, as shown in table II, these alterations comprise a

decrease in the blood pH, a slight fall in the alkaline reserve and an increase in the carbon dioxide tension. It will be noted, however, that the pH in the series studied averaged 7.20 and in no instance fell below 7.15.

If we now turn to table III, in which our results in asphyxiated babies are listed, we find alterations in the acid-base balance of these infants which are much more marked than those shown in table II and approach, or even exceed, the limits compatible with the existence of life.

TABLE III

Showing the oxygen and carbon dioxide relationships of foetal blood in six severely asphyxiated infants

In Cases 1, 2, and 3, the asphyxia proved fatal, although the heart sounds immediately after birth were clearly audible in each instance.

CASE NUMBER	MATERNAL VEIN				UMBILICAL VEIN				UMBILICAL ARTERY			
	pH	CO_2 content	CO_2 tension	O_2 content	pH	CO_2 content	CO_2 tension	O_2 content	pH	CO_2 content	CO_2 tension	O_2 content
1					6.95	35.1	69.4	0.6		36.0		0.0
2	7.18	39.0	45.2	9.8	7.05	34.6	54.6	1.3				
3					6.95	38.4	75.9	0.0		38.5		0.0
4					7.12	37.0	49.5	0.8		37.4		0.2
5	7.20	36.2	40.3	10.7	7.06	40.0	61.7	2.1				
6					7.08	39.7	58.7	2.9				
Average					7.04	37.5	61.6	1.3				

The figures for oxygen and carbon dioxide content are expressed as volumes per cent and those for carbon dioxide tension in mm. of mercury.

Oxygen content

Of the several blood chemical changes demonstrable in asphyxia neonatorum, the decrease in the oxygen content of the blood must be regarded as the primary alteration from which the others in large part follow. Our results listed in table II show that the oxygen content of the umbilical vein blood at birth may occasionally fall to 5 volumes per cent without the infant showing clinical evidence of asphyxia; on the basis of Huggett's figures (referred to above), this would indicate that the mixed blood reaching the respiratory center in these cases contains approximately 2.5 volumes per cent of oxygen,

which would correspond with an oxygen tension of less than 20 mm. of mercury. Just how long life may be sustained by the foetus at such low levels of oxygen tension cannot be said. It seems clear, however, that as soon as the oxygen content of the umbilical vein blood drops much below this figure, some unknown alteration ensues in the functional activity of the foetal brain cells which results in the clinical picture of asphyxia neonatorum, and in case the blood becomes even further reduced, to one volume per cent of oxygen or less, this tissue change becomes irreversible and the infant succumbs despite all efforts at resuscitation. Carl F. Schmidt (15) has designated this tissue change as the *reversal* and believes it to be due to an accumulation of products of incomplete oxidation within the cells of the respiratory center. In a series of clear-cut experiments he has shown that brain cells which have undergone this change lose their power of utilizing oxygen, so that following the *reversal*, restoration of oxygen supply may fail to restore functional activity because the altered cells are no longer able to absorb oxygen from the blood. He has also demonstrated that when the respiratory center is on the verge of the *reversal*, that is, when the oxygen supply is barely adequate for the basal requirements of the cells, the usual respiratory stimulants, such as atropine, camphor, strychnine, caffeine, as well as carbon dioxide, become depressant, rather than stimulant, and actually precipitate the *reversal*, or respiratory failure; electrical stimulation under similar circumstances has the same effect. The experimental evidence, then, indicates that only in the presence of an adequate supply of oxygen are respiratory stimulants effective, while in the absence of suitable amounts of this gas they may even be deleterious.

Carbon dioxide content

It may be seen from table III that the carbon dioxide content of the blood in our cases of asphyxia neonatorum was consistently low, averaging 12 volumes per cent less than that found in normal newborn infants and 7 volumes per cent less than was met in babies born under anaesthesia. These findings are the direct reverse of those reported by Kane and Kreiselman (7), who state that their asphyxiated babies showed a high carbon dioxide content. It seems likely that an explanation of this discrepancy may be found in the fact that

our cases were particularly severe examples of this condition, while those of Kane and Kreiselman were milder and hence failed to show some of the characteristic changes. We feel doubly certain that the carbon dioxide content of the foetal blood does fall in severely asphyxiated infants because of the very high values for blood lactic acid which these cases show, exceeding in some instances 80 mg. per 100 cc., in contrast to the normal figure at birth of 35 mg. per 100 cc. If now this excess lactic acid (45 mg. per 100 cc.) be expressed in terms of millimols per liter, it will be found that the additional lactic acid would unite with about 5 millimols of base, and in so doing would displace the same amount of carbon dioxide. The average fall of 11 volumes per cent in the total carbon dioxide content, which we report in these cases, would correspond with a release of some 4.4 millimols of carbon dioxide bound by base, a figure in close agreement with the one calculated. In individual cases, moreover, we have found that an increase of 4 mg. in the blood lactic acid of the foetus is accompanied by a diminution in carbon dioxide content of approximately one volume per cent. We accordingly regard the low carbon dioxide content of the blood in asphyxia neonatorum as a characteristic and necessary result of the introduction into the blood stream of large amounts of lactic acid. Our complete figures for the blood lactic acid of normal and asphyxiated infants have appeared in a previous paper (9).

pH and carbon dioxide tension

One of the most striking characteristics of asphyxia neonatorum from a blood chemical viewpoint is the marked decrease in the pH of the serum. As shown in table III, the serum pH of deeply asphyxiated infants descends to the very lower limit of the maximum tolerated pH range, and in two of our three fatal cases actually fell below 7.00. In other words, these babies are in a state of true, uncompensated acidosis. The nature of this acidosis is shown more precisely in chart 1, in which we have utilized the graph devised by Van Slyke and have charted upon it the $BHCO_3$ millimolecular concentrations and the pH values of normal, anaesthetized and asphyxiated babies. It appears from this graph that the acidosis of asphyxia neonatorum is essentially one of uncompensated alkali deficit, but at the same time

it should be noted that several of the points charted for asphyxiated babies fall close to the adjacent area of uncompensated carbon dioxide excess, and had our estimations of the $BHCO_3$ concentrations been made upon serum rather than upon whole blood, they would have encroached still more upon this territory. In view of these facts, it

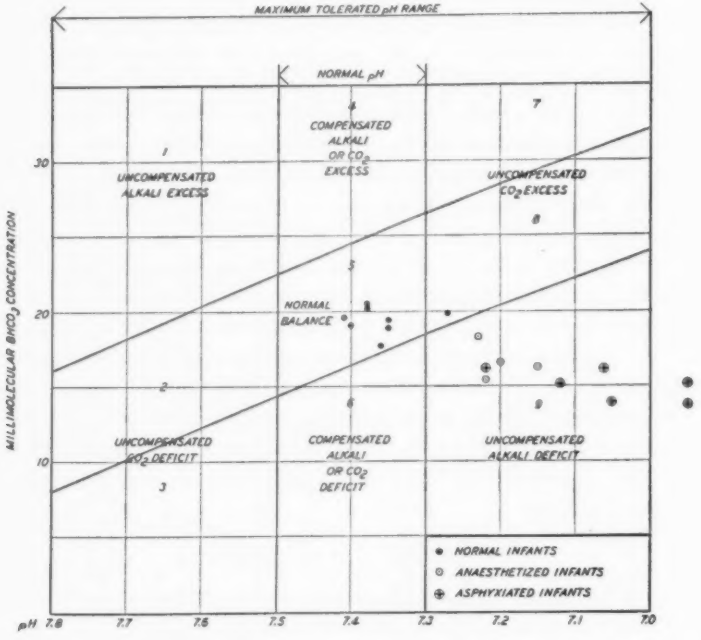

CHART 1. SHOWING THE ACID-BASE EQUILIBRIUM OF THE BLOOD IN NORMAL, ANAESTHETIZED AND ASPHYXIATED INFANTS, AS PLOTTED ON THE GRAPH DEVISED BY VAN SLYKE

seems probable that the acidosis in this condition results from a combination of two factors, (1) an alkali deficit due to fixation of base by lactic acid and (2) a primary carbonic dioxide excess as the result of inadequate diffusion of this gas from foetus to mother.

COMMENT

We believe that the evidence which has been presented justifies certain definite conclusions in regard to the treatment of asphyxia neonatorum. In the first place, since the tension of carbon dioxide in the blood of asphyxiated infants is usually almost twice that found in normal babies, the use of this gas as a resuscitating agent seems to us superfluous and possibly harmful, inasmuch as it may tend to intensify an already existing acidosis. Secondly, since the oxygen content of the blood in asphyxia neonatorum is so low as to be inadequate for basal metabolic needs, it seems altogether likely, in view of the experimental work of Schmidt, that the usual forms of stimulation (including slapping, bathing and carbon dioxide inhalation) produce depression rather than excitation of the respiratory center and may even result in irreparable damage to the brain cells.

There seems to be only one urgent indication in the treatment of asphyxia neonatorum, and that is to introduce oxygen into the circulating blood of the infant. Whether this is effected by manual artificial respiration, by mouth to mouth breathing, or by some form of apparatus such as the Drinker respirator, seems to us of minor importance, so long as the air passages have been carefully cleared of mucus and a constant supply of oxygen (or air) is maintained into the pulmonary alveoli. If physical stimulation must be employed, it should not be used when the baby is cyanotic, but only when, as the result of oxygenation, it has become pink.

The exact cause of the onset of respiration at birth, as well as the nature of intra-uterine apnea, remains obscure. The relatively high carbon dioxide tension of foetal blood as it exists *in utero* seems difficult to reconcile with a state of apnea, and at present this phenomenon can only be explained by assuming that the sensitivity of the foetal respiratory center, in respect to this gas at least, is markedly depressed.

CONCLUSIONS

1. The carbon dioxide tension of foetal blood is normally higher than that of the maternal arm vein, the carbon dioxide diffusion gradient between foetus and mother being about 1.3 to 1.

2. The elevated carbon dioxide tension of the mixed foetal blood supplying the brain of the foetus, is difficult to reconcile with the

apneic state of the foetus *in utero* and at present necessitates the assumption that the sensitivity of the foetal respiratory center, in respect to carbon dioxide at least, is definitely depressed.

3. The primary blood chemical change in asphyxia neonatorum is a reduction in the oxygen content of the foetal blood to extremely low levels, the blood of the umbilical vein falling in fatal cases below one volume per cent.

4. The carbon dioxide content of the blood in severe asphyxia neonatorum is slightly lowered as a result of the displacement of this gas from base by the large amounts of lactic acid present.

5. The serum pH of asphyxiated infants is reduced to the lower limits compatible with life, and in fatal cases may even fall below 7.00.

6. The evidence indicates that the use of carbon dioxide as a resuscitating agent in asphyxia neonatorum is not only superfluous but may even be harmful in that it tends to aggravate an already existing acidosis. It is further suggested that other attempts at stimulation, such as slapping and tubbing, may also be deleterious.

7. The conclusion is reached that the chief therapeutic indication in asphyxia neonatorum is for oxygen (or air); the particular method by which the oxygen is administered seems of minor importance, so long as the air passages are clear and the pulmonary alevoli are supplied with adequate amounts of this gas.

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BOOK REVIEWS

Statistical Methods for Research Workers. By R. A. FISHER, Sc.D. Second edition revised and enlarged. 269 pp. (*Oliver and Boyd, Edinburgh, 1928.*)

A revision of the 1925 edition of this book. It outlines for the research worker, especially in the biological field, methods of analysing his quantitative data. The principal change in this edition is the expansion into an additional chapter of the author's method of maximum likelihood in statistical estimation.

L. J. R.

Mikroplastik (mikrobielle kolloïde Plastik). By R. GRASSBERGER. Abhandlungen aus dem Gesamtgebiete der Hygiene. Heft 3. (*Leipzig, Deuticke, 1929.*)

This is a lecture describing the phenomenon of clouding which occurs in bacteriological, nutrient gelatin. Usually two distinct zones of clouding occur in inoculated tubes of gelatin. The phenomenon seems to be related to the oxygen tension, to acid formation and to other metabolic products.

W. M. C.

Clinical Nutrition and Feeding in Infancy and Childhood. By I. NEWTON KUGELMASS, M.D., Ph.D., Sc.D. 345 pp. $6.00. (*J. B. Lippincott Company, Philadelphia, 1930.*)

This is an attempt to present in concise and easily available form the modern methods of feeding during infancy and childhood. In addition to the discussion of normal infant feeding, the digestive disturbances and the deficiency diseases, there are sections on the dietary treatments of diabetes, epilepsy, acid-base disturbances, blood diseases, nephritis, the allergic diseases, and others. In each section there are tables of calculated diets which are helpful. In many ways this is a valuable handbook for the practitioner, but unfortunately Kugelmass persists in presenting as facts many theories which are as yet unproved.

L. W.

Historic Artificial Limbs. By VITTORIO PUTTI, M.D. With illustrations. (*Paul B. Hoeber, New York, 1930.*)

Every one who has ever taken a course in college in German literature must have heard of that stalwart old warrior, Goetz von Berlichingen, and his iron hand. In my own undergraduate days it never occurred to me that Goetz wore some kind of an artificial arm. It is most interesting, therefore, to find at the beginning of this book photographs of the hero's iron arm and hand. After describing this, the writer brings together other examples of historic artificial limbs. Some of them he finds pictured on vases; others are mentioned in various medieval chroni-

cals. Especially interesting is the iron left hand described by Ambroise Paré which was constructed in the sixteenth century by an artificer called "Le petit Lorrain." The fingers of this hand are moved by ratchets that are attached to metal levers. The rest of the book is taken up with a description of artificial limbs that may be seen in Florence in the Stibert Museum. Stibert was one of those wandering Englishmen who lived for a long time in Italy and collected weapons of every age in every country. He left his possessions to the English Government which, however, refused the bequest. Stibert's collection was then given to the city of Florence. This little book on artificial limbs is the only treatise dealing with this special subject. The illustrations are excellent.

J. R. O.

Clio Medica. A Series of Primers on the History of Medicine. Edited by E. B. Krumbhaar, M.D. (*Paul B. Hoeber, Inc., New York, 1930–31.*) The Beginners: Egypt and Assyria—by Warren R. Dawson. Medicine in the British Isles—by Sir D'Arcy Power. Anatomy—by George W. Corner. Internal Medicine—Sir Humphrey Rolleston, Bart. Physiology—John F. Fulton.

Nothing is more difficult than to write the concise history of a large field of human endeavor. Almost any aspirant for a doctor's degree can pick out some very restricted field and exhaust it without much difficulty. On the other hand, a general description of some entire subject or period requires the mind of a master as well as of a scholar, who not only knows intimately the entire subject, but is able to present the important elements in it without over-loading his book with secondary detail. Nothing therefore is harder to write than a primer. There have been in the past some successful efforts of this kind. No one except Professor Charles Singer with his detailed knowledge of medical history could have written his Short History of Medicine or his still smaller book on Greek and Roman Medicine and Biology.

The first five volumes of Clio Medica, as this new series of primers on the history of medicine is called, present a new proof, if proof were needed, of the increasing interest among physicians in the history of their own profession. The first volume which deals with Primitive Medicine and the Medicine of Egypt and Assyria is the work of Dr. Warren R. Dawson and gives, in the first three chapters, the primitive ideas of disease and of death: a description of primitive means of diverting death and prolonging life and finally a sketch of the medical man as the magician. There follows a very clear outline of ancient Egyptian medicine and the medicine in the Assyrio-Babylonian Empire. At the end of the book is a useful bibliographical note in which any reader may find a list of the most important works on the subject. Anyone who has read this little book will, I believe, be led on to further reading.

Medicine in the British Isles is treated by Sir D'Arcy Power. Those who were fortunate enough to hear Sir D'Arcy lecture while he was Visiting Lecturer at our

Institute of the History of Medicine will need no urging to read the primer that he has written. Especially useful for the beginner is the chapter on "Some Masters of British Medicine" and even those of us who think that we know something already may get new facts from the chapter on "Medical Education."

Dr. George Corner, who is responsible for the volume on Anatomy, is already known to historical students for his researches among the anatomical treatises of the school of Salerno. The illustrations in his primer are unusual and most helpful, while his list of sources will furnish the ordinary reader with material enough for his next twenty years' reading. The chapter on Anatomy in the Middle Ages is an excellent example of how to give the general outline of a complex period without over-loading and yet without serious omissions.

Sir Humphrey Rolleston has written the primer on Internal Medicine. It contains no bibliographical material, but one does not miss a list of references, in as much as almost all the important authors and their works are mentioned in the course of the book. It is almost impossible in dealing with a subject of this kind to avoid a certain amount of dryness. There are so many names and so many dates that claim a place. Nevertheless, Sir Humphrey has managed to avoid being dull without falling into the opposite fault of omitting important material.

Perhaps the most stimulating and interesting of all the primers published thus far is Dr. John Fulton's Physiology. If Dr. Fulton had written nothing except his primer he would have proved himself a complete master of the subject with which he deals. There is a balance and a harmony about this little book on Physiology which reaches a level of excellence that it will be difficult for other writers in the series to attain. The chapters on Digestion and more especially the chapter dealing with the Rise of the Teaching Laboratories seemed to the reviewer even better than the rest of the book although it is probably the reviewer's own fault that he did not find the other chapters quite as stimulating as these.

The editor, Dr. Krumbhaar, is to be most heartily congratulated on the volumes that have appeared thus far. Mr. Hoeber the well known medical publisher has added a new success to his many achievements, in publishing this new series of primers on the history of medicine.

J. R. O.

Tropical Medicine in the United States. By ALFRED C. REED, M.D. 410 pp. $6.00. (*J. B. Lippincott Company, Philadelphia, 1930.*)

This book contains nine chapters whose contents may be judged by their titles as follows: Protozoal Diseases; Spirochetal Diseases; Bacillary Diseases; Helminthic Diseases; Diseases of Unknown Etiology; Mycotic Diseases; Metabolic Diseases; Arthropod Diseases; and Miscellaneous. The last chapter includes sections on tropical ulcers, heat disease, personal hygiene, and tropical climatology. Among the diseases described are amebiasis, malaria, relapsing fever, bacillary dysentery, plague, undulant fever, leprosy, hookworm disease, schistosomiasis, yellow fever, dengue, typhus, sprue, mycetoma, blastomycosis, beriberi and pel-

lagra. The causative organisms, in the case of the parasitic diseases, are described as well as symptomatology, pathology, treatment and methods of prevention and control. It is impossible to include an exhaustive treatment of so many diseases in one small volume, but the author has succeeded very well indeed in attaining his objective which he states in his preface to be "to present a serviceable guide to the physician in the United States in his contacts with tropical medicine."

R. H.

Manual of Physical and Clinical Diagnosis. By OTTO SEIFERT and FRIEDRICH MUELLER. Translated by E. Cowles Andrus. Associate in Medicine, Johns Hopkins University, Associate Physician, John Hopkins Hospital. Pp. 543. $6.00. (*J. B. Lippincott Company, Philadelphia and London, 1930.*)

Into this vade-mecum, fashioned to a size to fit one's coat pocket, is packed a summary of the whole subject matter bearing upon medical diagnosis by bedside and laboratory methods. At the end are brief surveys of cutaneous diseases, poisons and therapy therefor, and tables indicating the solubility and dosage of drugs. There is even a description of watering-places, with analyses of spring waters. Though this very complete volume contains 543 pages, the whole is of very convenient pattern and is the meatiest medical publication we have ever had the pleasure of reading.

Otto Seifert, late Professor of Medicine at Wuerzburg, and Friedrich Mueller, whose Munich clinic has for so long been the Mecca of Americans, need no laudation here. The fact that they wrote the book indicates the soundness of authority of the observations upon clinical medicine and the authenticity of description of laboratory procedures. We have been familiar with various small compendiums that embrace one or more restricted fields of medicine, but Seifert and Mueller's book is unique in its satisfying completeness.

Though twenty-four editions have been printed in German, Dr. Andrus has contributed substantially to the Anglo-American medical literature by bringing out this English translation. With a few negligible exceptions the English phrasing is very convincing and lacks the stilted style of many translations. The translator has also made note of certain "procedures to which the American student and physician are accustomed" in a very judicious manner, thereby enhancing the usefulness of the translation in this country. For example, his notes on the Van den Bergh reaction, recent developments in connection with the etiology of yellow fever, (the authors had quoted Noguchi's work without comment), the classification of pneumococci and arrangement of blood groupings, are excellent.

The authors state that "aegophony" is met with over the compressed portion of lung adjacent to the upper margin of a pleural exudate. This might suggest to the student that aegophony is to be heard best immediately beyond the bounds of a pleural effusion. Laennec's experience was that aegophony is most typical just *below* the upper level of fluid, notably below the angle of the scapula. Perhaps

the authors intended to convey a description in accord with that of Laennec, but it is not altogether clear. The section devoted to the consideration of heart murmurs could be made much more valuable by the addition of suitable descriptions of cardio-respiratory and accidental murmurs. The authors are content to let the differentiation of functional and organic mitral murmurs rest upon the presence or absence of the "other evidences of valvular disease;" such other evidences may be very difficult to determine. We should have welcomed also a note by authors or editor upon the recent great advance in the knowledge of undulant fever.

The student can not afford to be without this book, nor can this reviewer; in this he will be found to represent a very large part of the American medical profession.

J. T. K., JR.

The Proceedings of the Charaka Club. Vol. VII. (*Paul B. Hoeber, New York, 1931.*)

The latest volume of the Proceedings of the Charaka Club is made up of an amazing collection of articles and verses. These efforts, mainly non-medical, deal in a very haphazard way with anything from Norman ornamentation and scattering seeds to a tired doctor's prayer. Edward C. Streeter alone excuses the existence of the book by his study of the "Education of the Barber Surgeons of France." He deals with the crude make-up of the Barber Surgeons and the importance of the scholastic studies at Montpellier, Paris, and Lyons. It is regrettable that the remaining essays in this volume are so trite in substance, and that the verse is below the newspaper average, out of 34 contributions, only three others are of medico-historical content, and those are mediocre.

M. P.

History of Haitian Medicine. By ROBERT P. PARSONS, Lieut.-Com., M. C., U. S. N. Foreword by Edward R. Stitt, Rear Admiral, M. C., U. S. N. 196 pp. $2.25. (*Paul B. Hoeber, Inc., New York, 1930.*)

In the development of the history of medicine, the smaller isolated countries have not received their proper share of attention. Recently, however, the background of medicine in Haiti has been studied by Dr. Parsons. In this study we find medical and sociological experiments on a large scale. Dealing with an isolated community, cause and effect stand out very clearly, and results have more definite meaning than other large scale experiments in less isolated communities.

This history divides itself into three periods, the period of French occupation in the 17th and 18th centuries, the period of native independence from 1804 and 1915, and the period of American occupation since 1915. The first era is marked by the introduction of smallpox which destroyed the native Indian population, the importation of slaves and their African diseases and Voodoo Magic medicine, and the spread of yellow fever. It was yellow fever that brought to an end French rule, for they were defeated more by this disease than by the rebellious natives.

Medically, the time of native independence was totally non-productive. Handicapped by the lack of political stability and lack of proper training "medical practice was characterized in the main by the basest and most vicious form of charlatanry. What were called hospitals were unspeakable." During this period a few names do stand out, but it was not until the American occupation in 1915 that any serious attempt was made to introduce modern medical methods into Haiti.

Under the leadership of the medical corps of the Navy, conditions were notably improved in a short space of time. The introduction of modern hospitals, public health measures and better medical education brought about reforms that have changed completely the medical aspects of that country. The successful attempt to eradicate yaws was one of the most important results of this work.

The chapter on Haitian doctors is very interesting in view of the increasing desire to establish medical schools for the training of "natives" in other countries. Dr. Parsons concludes that the Haitian doctors are capable of acquiring knowledge and skill and are able to apply this knowledge and skill to practical problems. But their lack of ability to organize and administrate would defeat any national public health program under native leadership. Also, they lack a consciousness of medical ethics and a scientific investigative spirit. "They are content to accept empiricism and authority in medicine. Originality, a scientific approach, scientific ideas, scientific observations and interpretations, carefully planned and controlled experiments—these are not possible." So when American occupation ceases, a fourth phase of Haitian medicine will begin, possibly retrogressive changes will take place from our viewpoint. "Perhaps the occupation has been too zealous, perhaps it has been attempting to install a high-powered motor in an ox-cart not built to stand the strain or the speed. American efficiency is one thing. Haitian culture is another."

C. L. G.